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Enantiomerically Pure 3-Oxa-2.7-diazabicyclo[3.3.0]octanes: Preparation, Analysis of Conformation and Test for Enantioselective Catalysis

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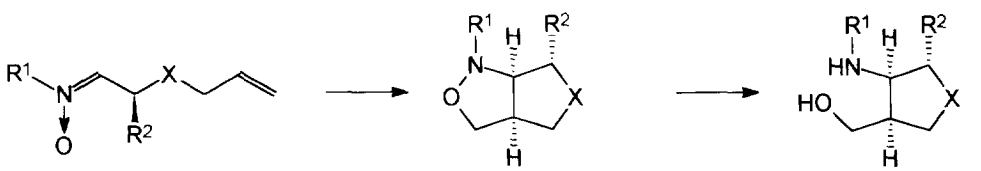
Abstract: Amino alcohols **5** were prepared by various methods starting from (*S*)-(+)-alanine and (*S*)-(+)-valine. Swern oxidation of **5** afforded aldehydes **6** which were treated without isolation with N-alkylhydroxylamines to give nitrones **7A, B**. These underwent spontaneously an intramolecular cycloaddition yielding 3-oxa-2.7-diazabicyclo[3.3.0]octanes **9A, B**. The oximes **8C** obtained by reaction of **6** with hydroxylamine were converted to compounds **9C** in toluene at 110°C. Products **9** were obtained enantiomerically pure. X-ray analyses were performed with **9Ac** and **Bc**. The NMR coupling constants of **9Ac** and **Bc** are in good agreement with those calculated from the torsional angles detected by the X-ray analyses. Thus, their conformation in solution resembles the conformation in the crystalline state. The majority of compounds **9** exists in a similar conformation as the NMR data indicate. On the other hand, substituents at position 4 or 5 in compounds **9** give rise to an inversion of conformation. In compounds **10** and **11** two 3-oxa-2.7-diazabicyclo[3.3.0]octane units are connected by an ethylene bridge. Reduction of compounds **9** yielded pyrrolidines **12**. 2.7-Diazabicyclo[3.3.0]octane **14** was obtained via **13** by reduction starting from **9Ag**. Compounds **9-12** and **14** were tested as catalysts for the reaction of diethylzinc with benzaldehyde. This reaction was catalyzed effectively by all compounds, however, the enantiomeric excesses did not exceed 61%.

Among the intramolecular 1.3-dipolar cycloadditions of alkenyl nitrones the reaction of C-4-pentenyl nitrones (5-hexenylimine-N-oxides) as **1a** is unique with respect to several points.[1] With a very few exceptions the cycloaddition of such nitrones proceeds with high regioselectivity affording only fused products as **2a** in contrast to other alkenyl nitrones which often give a mixture of fused and bridged cycloaddition products. The same is true with respect to the stereoselectivity. The cycloaddition products of the 5-hexenylimine-N-oxides are only obtained as cis-fused bicyclic compounds, since two trans-fused five-membered ring compounds would suffer from severe steric strain. Furthermore, a substituent at 2-position of the 5-hexenyl-imine-N-oxide gives rise to an effective asymmetric induction controlling the formation of two new stereogenic centers at position 1 and 5 in the bicyclic products at least (see **2a**).



1 **2** **3**

a: X = CH_2
b: X = NR^3

By this process a trans relationship at positions 1 and 8 is usually caused. Thus from enantiomerically pure starting materials optically active 3-oxa-2-aza-bicyclo[3.3.0]octanes are available.[1a,b] Reductive ring opening furnishes corresponding cyclopentyl derivatives **3a**.

The same is true for imine-N-oxides in which one of the carbon atoms of the 5-hexenyl chain is replaced by a heteroatom.[2] Starting from enantiomerically pure α-amino acids we generated 3-aza-5-hexenimine-N-oxides **1b** which underwent spontaneously an intramolecular cycloaddition affording 3-oxa-2.7-diazabicyclo[3.3.0]octanes **2b** which were proven to be enantiomerically pure. Reductive opening of the isoxazolidine ring made enantiomerically pure 3-amino-4-hydroxylmethyl-pyrrolidines **3b** available.[3]

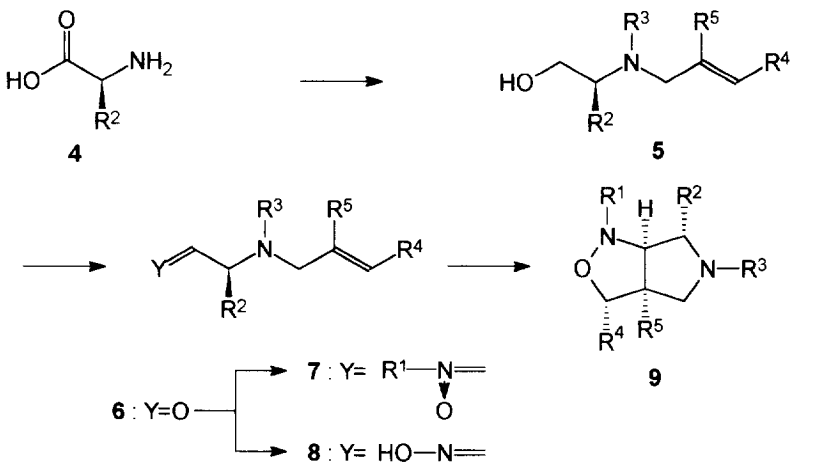
During the last years a number of α.β-diamines has been used successfully as catalysts in enantioselective syntheses.[4] In compounds **2b** a rather rigid α.β-diamino moiety is present, whereas in the pyrrolidine derivatives **3b** the diamino moiety is somewhat more flexible. In principle both of these compounds should be appropriate for enantioselective catalysis. Thus we decided to test bicyclic compounds **2b** as well as pyrrolidines **3b** as catalysts in the reaction of benzaldehyde with diethylzinc.[4a,c,d] For this reason we prepared a number of such compounds modifying their substitution pattern in different ways. Here we report on these attempts although the results in the enantioselective catalysis were finally disappointing.

Preparation of Enantiomerically Pure 3-Oxa-2.7-diazabicyclo[3.3.0]octanes **9**

Starting from (*S*)-(+)-alanine or (*S*)-(+)-valine we prepared the α.β-amino alcohols **5** by different methods. Most simply, compound **5a** was synthesized by double allylation of valine with allyl bromide followed by reduction with lithium aluminum hydride.[3] Introduction of a single allyl group was achieved by reaction of valinol[5] with allyl bromide (**5d**). Reaction of the amino acids with benzaldehyde furnished imines which were reduced by sodium borohydride affording N-benzyl amino acids.[6] These were treated with allyl bromide. Subsequent reduction of the products with lithium aluminum hydride gave amino alcohols **5b** and **c**. Compounds **5f** and **g** were prepared by reversal of the last two reaction steps. At first, N-benzyl alanine was reduced by a mixture of lithium borohydride and trimethylsilyl chloride[5] to give N-benzyl alaninol which was finally treated with 3-chloro-2-methyl-1-propene or ethyl 4-bromo crotonate, respectively. Amino alcohol **5e** was obtained by treatment of **5d** with tosyl chloride. The amino alcohols **5a-g** were converted to the corresponding aldehydes **6** by Swern oxidation.[7] Without isolation the aldehydes **6** were treated with N-alkylhydroxylamines or unsubstituted hydroxylamine. The nitrones **7A, B** formed with N-tert-butyl or N-benzylhydroxylamine, respectively, underwent spontaneously an intramolecular cycloaddition affording the bicyclic compounds **9A** and **B**, respectively. The oximes **8** were converted to compounds **9C** by heating in toluene at reflux.[3,8] Treatment of **9Ca** with tosyl chloride afforded compound **9Da**.

The conversion of the α-amino acids (*S*)-(+)-alanine and (*S*)-(+)-valine to the 3-oxa-2.7-diazabicyclo[3.3.0]octanes **9** on the reaction path described above proceeded without racemization affording enantiomerically pure products.[3]

This was confirmed by the NMR spectra of the salts formed from compounds **9Aa, Ab,Ac,Af Ba, Bc, Be** and **Cb** by treatment with (*S*)-(+)-O-acetyl mandelic acid[9] in deutero chloroform solution. These spectra showed no signal of a second diastereomeric salt that should have been formed if the second enantiomeric form of compounds **9** was present. Exactly such signals were found in the spectra of the salts formed from racemic compounds **9Aa** and **Cb** by treatment with (*S*)-(+)-acetyl mandelic acid. In these spectra clearly separated



	R^1		R^2	R^3	R^4	R^5		R^2	R^3	R^4	R^5
A	tBu	**a**	iPr	Allyl	H	H	**e**	iPr	Tos	H	H
B	Bzl	**b**	iPr	Bzl	H	H	**f**	Me	Bzl	H	Me
C	H	**c**	Me	Bzl	H	H	**g**	Me	Bzl	CO_2Et	H
D	Tos	**d**	iPr	H	H	H	**h**	Me	Bzl	CH_2OH	H

Isolated Compounds **9** (% yield): **Aa** (78)[3], **Ab** (38)[3], **Ac** (45)[3], **Ad** (29), **Af** (55), **Ag** (61), **Ah** (59), **Ba** (51)[3], **Bc** (54)[3], **Be** (50), **Bf** (58), **Ca** (64)[3], **Cb** (64), **Da** (76). - **9Ah** was obtained by reduction of **9Ag** with $LiAlH_4$. -

Reaction **4** → **5**: **a**: 1. C_3H_5Br, 2. $LiAlH_4$ - **b, c**: 1. PhCHO, 2. $NaBH_4$, 3. C_3H_5Br, 4. $LiAlH_4$, **d**: 1. $LiBH_4/Me_3SiCl$, 2. C_3H_5Br- **f, g**: PhCHO, 2. $NaBH_4$ 3. $LiBH_4/Me_3SiCl$, 4. CH_2=C(Me)-CH_2Cl or trans EtO_2C-CH=CH-CH_2Br, respectively. - **5e** was obtained from **5d** and TosCl.

Reaction **5** → **7**, **8**: 1. DMSO, $(COCl)_2$, Et_3N, 2. R^1NHOH (**7**) or H_2NOH (**8**), respectively.

signals of the two diastereomeric salts appeared due to the following groups: **9Aa**: both the two CH_3 of *i*Pr, *t*-Bu, 6β-H and 8-H; **9Cb**: both the two CH_3 of *i*Pr, one of the benzylic hydrogen atoms, 4α-H and 1-H. Furthermore, enantiomerically pure **9Ca** as well as the racemic compound were treated with (*S*)-3.3.3-trifluoro-2-methoxy-2-phenylpropionyl chloride (Mosher chloride).[10] Again the spectra of the reaction product formed from the racemic mixture showed a large number of signals due to the second diastereomer which did not appear in the spectrum of the product obtained from the enantiomerically pure **9Ca**.

The Conformation of the Bicyclic Compounds 9

Compounds **9** were characterized in particular by their ^1H and ^{13}C NMR spectra (see Table 2). Furthermore, X-ray analyses of compounds **9Ac** and **Bc** were performed. Selected torsional angles are given in Table 1.[11]

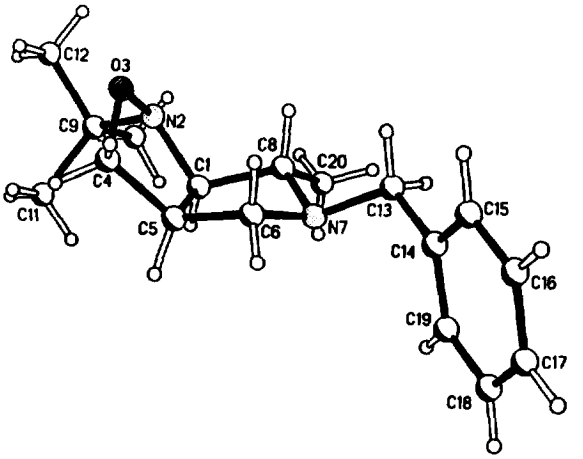


Figure 1. Molecular plot of (*1R,5R,8S*)-(+)-7-benzyl-2-*tert*-butyl-8-methyl-3-oxa-2.7-diaza-bicyclo[3.3.0]octane (**9Ac**).

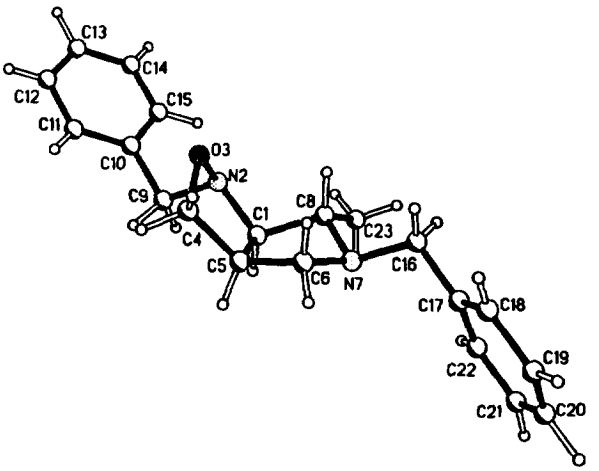


Figure 2. Molecular plot of (*1R,5R,8S*)-(+)-2.7-dibenzyl-8-methyl-3-oxa-2.7-diazabicyclo[3.3.0]octane (**9Bc**).

Table 1. Selected Torsional Angles of Compounds **9Aa** and **9Bc** [°] and ^{1}H NMR Coupling Constants Calculated from Those Compared to the Experimentally Found [Hz].

Torsional Angles φ	**9Ac** [°]	$^3J_{calcd}$ [a]	$^3J_{found}$	**9Bc** [°]	$^3J_{calcd}$ [a]	$^3J_{found}$
H(1)-C(1)-C(5)-H-(5)	0.1(4)	8.2	9.2	-7.0(4)	8.0	8.8
H(1)-C(1)-C(8)-H-(8)	147.4(2)	6.5	7.0	155.8(4)	7.6	7.5
H(4α)-C(4)-C(5)-H-(5)	-20.4(3)	7.2	7.8	-18.0(5)	7.4	6.4
H(4β)-C(4)-C(5)-H-(5)	100.4(2)	0	3.1	102.9(5)	0.2	<1
H(5)-C(5)-C(6)-H-(6α)	-23.6(3)	6.9	9.1	-19.3(5)	7.3	8.3
H(5)-C(5)-C(6)-H-(6β)	-144.2(2)	6.0	7.7	-140.0(4)	5.3	7.9

[a] Calculated with the aid of the Karplus equation $^3J = 8.5\cdot\cos^2\varphi$ -0.28 for 0° to 90° and $^3J = 9.5\cdot\cos^2\varphi$ - 0.28 for 90° to 180° -

As the X-ray data reveal there are only small deviations in the structure of both compounds. A plane is formed approximately by the atoms C(1)-N(2)-C(4)-C(5) on one hand, and C(5)-C(6)-C(8)-C(1) on the other

hand in both compounds. The angle between the two planes was determined to be 60.51° (0.08) for **9Ac** and 59.77° (0.15) for **9Bc**. The oxygen atom O-3 is located above the first plane at the concave side, the nitrogen atom N-7 below the latter plane at the convex side of the molecule. From the torsional angles given in Table 1 the corresponding coupling constants ^3J of the ^{1}H NMR spectra were calculated with the aid of the Karplus equation.[12] Although the coupling constants detected from the ^{1}H NMR spectra are somewhat larger in most cases compared to those calculated from the X-ray analyses, there is a good agreement in the trend of the numbers. This agreement indicates that the conformation which compounds **9Ac** and **Bc** adopt in solution is very similar to that in the crystalline state.

Table 2. Selected ^{1}H NMR Data of Compounds **9** (in $CDCl_3$). (a) Chemical Shifts δ (in ppm), (b) Coupling Contants J (in Hz)[a)]

(a)

	1-H	4α-H	4β-H	5-H	6α-H	6β-H	8-H
9Aa	3.62	3.99	3.61	3.03	3.41	2.16	2.28
9Ab	3.66	3.95	3.58	2.99	3.17	2.11	2.44
9Ac	3.47	3.96	3.56	3.02	3.14	2.01	2.31
9Ba	3.37	4.04	3.64	3.12	3.49	2.03	2.24
9Bc	3.29	4.09	3.69	3.16	3.19	1.99	2.26
9Da	4.62	4.22	3.63	3.06	3.31	1.93	2.14
9Ca	3.66[b)]	3.32[c)]	3.82[d)]	2.90	3.29	1.90[c)]	2.05
9Cb	3.76[b)]	3.38[d)]	3.84[b)]	2.93	3.14	1.90[b)]	2.18
9Af	2.78	3.64	3.53	-	2.51	2.34	2.70
9Ag	3.35	-	4.22	3.01	3.01	2.51	2.74
9Ah	3.25	-	3.81	2.71	2.75	2.35	2.88
9Bf	2.77	3.85	3.74	-	2.74	2.21	2.37
9Ad	3.49	3.99	3.46	3.00	3.06	2.67	2.69
9Be	3.28	3.64	3.30	3.14	3.94	2.99	3.61

(b)

	*J*1/5	*J*1/8	*J*4α/5	*J*4β/5	*J*5/6α	*J*5/6β
9Aa	8.1	6.7	7.4	<1	9.2	7.6
9Ab	8.4	6.4	7.2	2.6	9.4	7.9
9Ac	9.2	7.0	7.8	3.1	9.1	7.7
9Ba	8.6	6.9	6.2	<1	7.3	9.0
9Bc	8.8	7.5	6.4	<1	8.3	7.9
9Da	8.2	7.0	6.5	<1	8.7	9.0
9Ca	8.4	6.8	~8	<1	~8	~8
9Cb	8.1	7.0	nd	<1	8.2	~7
9Af	-	3.8	-	-	-	-
9Ag	8.6	5.2	-	7.3	8.8	2.3
9Ah	9.1	4.1	-	2.9	6.9	2.0
9Bf	-	6.7	-	-	-	-
9Ad	5.0	nd	7.7	6.7	7.6	3.9
9Be	7.0	1.9	7.8	4.4	8.2	5.0

[a)] Additional chemical shifts and coupling constants see Experimental Part [b)] Slight line broadening [c)] Line broadening [d)] Strong line broadening

Thus we were encouraged to use the NMR data of the other compounds for predictions on the shape of the molecules. As the agreement of the chemical shifts and the coupling constants reveals compounds **9Aa, Ab, Ba** and **Da** all adopt a conformation which resembles that found for **9Ac** and **Bc**. The significant deviation in the chemical shift of 1-H observed for compound **9Da** is caused by the strong electron-withdrawing effect of the tosyl substituent at position 2. The large differences in the chemical shift of 6α-H and 6β-H (Δδ = 1.06-1.46

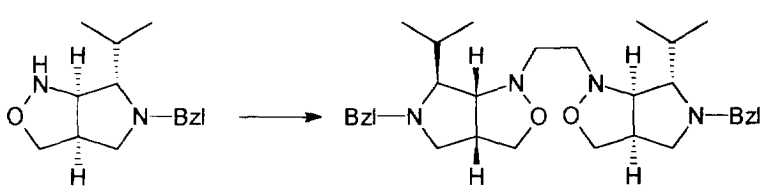
ppm) are most characteristic with respect to this conformation. These differences are due to a large high-field shift of the signal of 6β-H caused by the anti-periplanar position of the free electron pair of N-7 and this proton. The coupling constants ^3J 4α/5 are in the range from 6.0 to 7.5 Hz according to a torsional angle between 15 and 30°, whereas those of ^3J 4β/5 are smaller than 3.5 Hz due to an almost perpendicular arrangement. In contrast, the coupling constants ^3J 5/6α and ^3J 5/6β are both in the range from 7.3 to 9.4 Hz for these compounds.[13]

Substitution of the bicyclic compounds at position 4 (**9Ag, Ah**) or position 5 (**9Af, Bf**) gives rise to a conformational change as the smaller differences of the chemical shift for 6α-H and 6β-H indicate (Δδ = 0.17-0.53 ppm). This points to an inversion of the pyrrolidine ring. The N-7 is now in a position above the plane formed by C(8)-C(1)-C(5)-C(6) while 6α-H is put into a quasi-axial position almost anti-periplanar to the free electron pair of N-7. Thus its signal is shifted to higher field whereas that of 6β-H being now in a quasi-equatorial position undergoes a down-field shift. This conformational change is also reflected by the small coupling constants ^3J 5/6β of **9Ag** and **Ah**.[14] Concerning the isoxazolidine moiety the situation is complicated by the different effects of the substituents in these four compounds. However, it is assumed that the isoxazolidine moiety now adopts a conformation in which the oxygen atom is located at the convex side of the molecule below the plane formed by the four other atoms as was found for other 4-substituted 3-oxa-2.7-diaza-bicyclo[3.3.0]octanes.[13]

Broadening of several lines is observed in the spectra of compounds **9Ad** unsubstituted at N-2 and **9Ca, Cc** unsubstituted at N-7 indicating that interconversion of two conformers occurs. The similarity of the NMR data of **9Ad** with those of the 4- or 5-substituted compounds (**9Af-h, Bf**) suggests a similar conformation of these compounds and the major conformer of **9Ad**. On the other hand, the data of compounds **9Ca** and **Cc** resemble those of the bicyclic compounds which are unsubstituted at positions 4 and 5. Thus, the conformations of these compounds and the major conformer of **9Ca** and **Cc** should be similar. Finally, the compound **9Be** substituted with a tosyl group at N-7 obviously adopts a conformation that is neither in agreement with the one nor with the other group of the bicyclic compounds discussed so far.

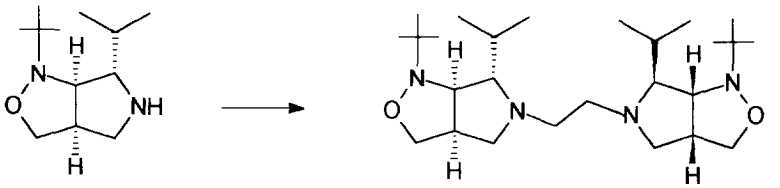
Reactions of Compounds ***9***

Two molecules of compound **9Cb** were joined across their 2-positions by treatment with oxalyl chloride to give a diamide which was reduced with a mixture of lithium borohydride and trimethylsilyl chloride[5] affording compound **10**. In a similar way compound **11** was synthesized in which the 7-positions of the two bicyclic fragments are connected by an ethylene bridge. For this purpose compound **9Ad** was treated with oxalyl chloride and the resulting diamide was subsequently reduced with lithium aluminum hydride.



9Cb **10**

1. $(COCl)_2$, K_2CO_3, 2. $LiBH_4$ / Me_3SiCl - yield: 16%

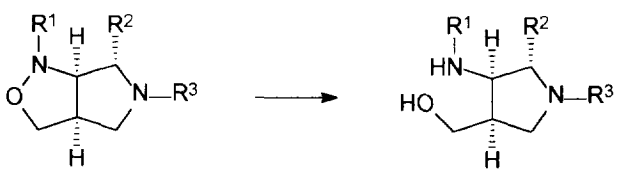


9Ad **11**

1. $(COCl)_2$, K_2CO_3, 2. $LiAlH_4$ - yield: 23%

The isoxazolidine ring of the bicyclic compounds **9** can be opened by reduction.[15] Thus, the pyrrolidines **12Aa, Ac** and **Da** were prepared by reduction of the corresponding compounds with zinc in acetic acid.[16] On the other hand, compound **12Bc** was obtained by hydrogenation of **9Bc** under pressure in the presence of a palladium hydroxide catalyst.[15] Reduction of **9Ag** with zinc in acetic acid furnished compound **13**. At first, the isoxazolidine ring is opened, however, in this case the amino group of the primarily formed 3-amino pyrrolidine compound attacks the ester function affording the hydroxy pyrrolidone moiety of **13**. Reduction of compound **13** with a mixture of lithium borohydride and trimethylsilyl chloride gave the 4-hydroxy-2.7-diazabicyclo[3.3.0]octane **14**.

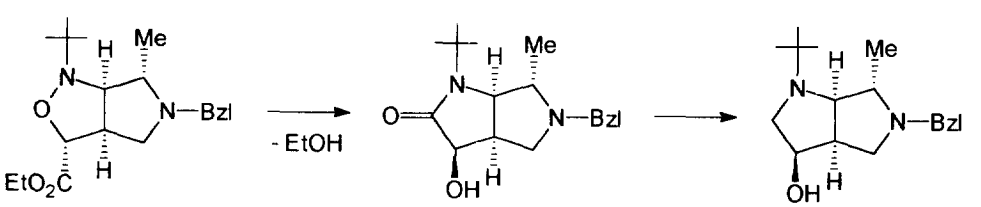
Again, these reactions proceeded without racemization. Thus, treatment of compounds **10, 12Ac, 12Da** and **14** with *S*-(+)-O-acetyl mandelic acid[9] afforded only one of the diastereomeric salts as was shown by their NMR spectra.



9 **12**

9 ⟶ **12** (% yield): **Aa** (42), **Ac** (74), **Da** (61): Zn / HOAc

9 ⟶ **12** (% yield): **Bc** (40): H_2 / $Pd(OH)_2$, 60°C, 81x10^5 Pa.



9Ag **13** **14**

9Ag ⟶ **13** (%yield): (62): Zn / HOAc **13** ⟶ **14** (% yield): (54): $LiBH_4$ / Me_3SiCl

Attempts on Enantioselective Catalysis

Compounds **9-12** and **14** were examined as catalysts in the reaction of diethylzinc with benzaldehyde. Usually, the reaction was performed at 0°C with addition of 6% of the catalyst in hexane solution. Under these conditions the reaction was effectively catalyzed, the yield of the 1-phenyl-1-propanol **15** exceeded 90% in every case. However, the determination of the optical rotation of **15** revealed that the ee's are far away from being satisfying. Reaction of **15** with *S*-(+)-O-acetyl mandelic acid and dicyclohexylcarbodiimide[17] afforded a diastereomeric mixture of compound **16**. Its diastereomeric excess and hence the enantiomeric excess of **15** was determined from the ^{1}H NMR spectrum of **16**. This was achieved by determination of the intensity ratio of the methyl signals of the propyl group at 0.63 and 0.88 ppm. The figures of the ee's are given in Table 3. With two of the best catalysts the reaction was also performed at -25°C affording somewhat better but again insufficient results.

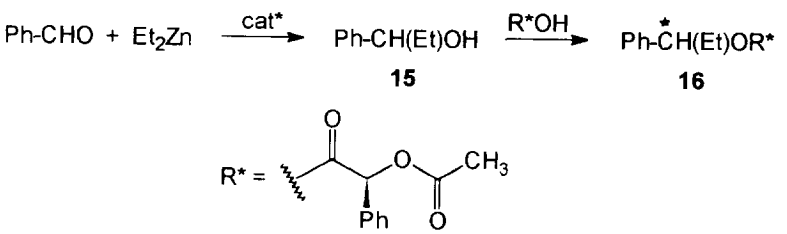


Table 3. Enantiomeric Excess in the Reaction of Benzaldehyde with Diethylzinc in the Presence of Catalysts **9, 10-12** and **14**[a]. (Enantiomer formed preferred)

9Aa	**9Ab**	**9Ac**	**9Af**	**9Ag**	**9Ah**[b]	**9Ba**[c]	**9Bc**	**9Be**	**9Bf**
13(R)	46(R)	40(R)	47(R)	19(R)	20(S)	42(S)	3(S)	6(S)	<10(S)
9Ca[d]	**9Cb**[b]	**9Da**	**10**	**11**	**12Aa**	**12Ac**	**12Bc**	**12Da**	**14**
45(S)	25(S)	0	19(R)	24(S)	18(S)	46(S)	28(S)	41(R)	15(S)

[a] Reaction conditions: 1.5 mol % Et_2Zn, 6% catalyst in hexane, reaction temperature 0°C, reaction time 24 h, [b] In toluene, [c] at -25°C ee = 61%, [d] at -25°C ee = 55%

Although the ee's were generally low, some interesting tendencies in the enantioselective effect of the catalysts can be observed. Whereas compounds **9A** (R^1 = tBu), with the exception of **9Ah**, afforded an excess of the (*R*)-enantiomer of **15**, with all of the compounds of **9B** (R^1 = Bzl) and of **9C** (R^1 = H) the (*S*)-enantiomer was obtained in excess. Replacement of the methyl group at position 8 (R^2) by the isopropyl group does not seem to affect the ee very much. However, if the allyl group (R^3) is replaced by the benzyl group opposite effects were found for the compounds **9A** (compare **9Aa** and **9Ab**) on the one hand and **9B** or **9C** on the other hand (compare **9Ba** and **9Bc**, **9Ca** and **9Cb**).

Surprisingly, compounds **9Ac** and **9Af** gave almost identical ee's although their conformation is quite different as discussed above. This result excludes the possibility that the conformation of the bicyclic compound is a priori crucial for the enantioselective efficiency. Neither **10** and **11** in which two bicyclic compounds are connected by an ethylene bridge nor the 2,7-diazabicyclo[3.3.0]octane **14** were found to give good ee's.

Finally, the 3-amino pyrrolidines **12** also did not give better results. It is only remarkable, that with **12Aa** and **Ac** the (*S*)-enantiomer of **15** was formed in excess whereas the corresponding bicyclic compounds **9Aa** and **Ac** furnished an excess of the (*R*)-enantiomer. On the other hand, with catalyst **12Da** the (*R*)-enantiomer was formed preferentially with an ee of 41%.

Generally, it seems that there are too much different effects influencing the enantioselectivity so that high ee's could not be reached by a directed modification of the substitution pattern.

Experimental Part

Elemental analyses were performed by the division Routine Analytik, Fachbereich Chemie, University of Marburg. Spectra were recorded with following instruments: NMR: Bruker AMX 500 and Bruker AC 300 using the residues of ^1H (δ = 7.24) or of ^{13}C (δ = 77.0 ppm) of the solvent $CDCl_3$ as internal standard. As far as not stated otherwise the ^1H NMR spectra were recorded at 300 MHz, the ^{13}C NMR spectra at 75 MHz. - MS: Varian CH 7 (EI) and 711 (FD). - IR: Beckman IR 33 and Bruker IFS 88-FT-IR. Optical rotations: Polarimeter Perkin Elmer 241, at 589 nm. - X-ray: 4-circle diffractometer (Enraf-Nonius CAD4).

Amino alcohols **5a-c** were prepared as described earlier.[3]

(S)-(+)-2-Allylamino-3-methyl-1-butanol (**5d**): Valine was reduced to valinol according to the procedure of Giannis and Sandhoff.[5] Then 7.9 g (61.1 mmol) of diisopropylethylamine and 3.7 g (30.6 mmol) of allyl bromide were added successively to 3.15 g (30.6 mmol) of valinol. The mixture was stirred at room temperature for two d. Afterwards the precipitate was filtered off, the organic layer was washed with water and dried over $MgSO_4$. Removal of the solvent afforded 2.3 g (61%) of **5d** (yellow oil). $[\alpha]_D^{22}$= 9.5° - IR (neat): 3380, 3100 cm^{-1}. - ^1H NMR: δ = 0.86 (d, 3H, CH_3); 0.91 (d, 3H, CH_3); 1.79 (d sept, 1H, 3-H); 2.43 (m, 1H, 2-H); 2.97 (s, 1H, OH); 3.26 (ddt, 1H, CH_2-CH=CH_2); 3.34 (dd, 1H, CH_2'-CH=CH_2); 3.34 (dd, 1H, 1-H); 3.57 (dd, 1H, 1-H'); 5.11 (m, 2H, CH=CH_2); 5.86 (m, 1H, CH=CH_2). - J(1/2) = 7.1, J (1'/2) = 4.2, J (3/CH_3) = 6.9, J (CH_2-CH=CH_2) = 5.9, J(CH_2'-CH=CH_2) = 7.1, ^2J(1/1') = 10.8, ^2J(CH_2-CH=CH_2) = 10.4, ^4J(CH_2-CH=CH_2) = 1.3 Hz. - ^{13}C NMR: δ = 18.4 (CH_3); 19.5 (CH_3); 28.7 (d, C-3); 49.8 (CH_2-CH=CH_2); 60.3 (C-1); 63.7 (C-2); 116.7 (CH=CH_2); 135.9 (d, CH=CH_2).

(S)-(-)-N-Allyl-N-(1-hydroxy-3-methyl-2-butyl)-4-tolyl sulfonamide (**5e**): 4.4 g (31.6 mmol) of K_2CO_3 and 3.0 g (15.8 mmol) of p-toluenesulfonyl chloride were added successively to a solution of **5d** in 100 mL of dichloromethane. After stirring the reaction mixture for two d the precipitate was filtered off, the organic layer was washed with water and dried over $MgSO_4$. After removal of the solvent and chromatography (Al_2O_3, Et_2O, R_f = 0.46), **5e** was obtained as a fade yellow oil in 26% yield (1.23 g). $[\alpha]_D^{25}$ = -38.5° - MS (FD): m/z = 297 (100) [M^+]. - IR (neat): 3480 cm^{-1}. - ^1H NMR: δ = 0.62 (d, 3H, CH_3); 0.84 (d, 3H, CH_3); 1.99 (m, 1H, 3-H); 2.34 (s, 3H, Ar-CH_3); 3.42 (dd, 1H, 2-H); 3.68 (dd, 2H, 1-H and CH_2-CH=CH_2); 3.89 (dd, 1H, CH_2'-CH=CH_2); 4.15 (dd, 1H, 1-H'); 5.13 (m, 2H, CH=CH_2); 5.82 (m, 1H, CH=CH_2); 7.21 (d, 2H, Ar-H); 7.67 (d, 2H, Ar-H). - J (1'/2) = 8.3, J (3/4) =6.6, J (3/CH_3) = 6.6, ^3J(CH_2'-CH=CH_2) = 6.3, ^2J(1/1') = 8.9, ^2J(CH_2-CH=CH_2) = 16.0 Hz. - ^{13}C NMR: δ =20.2 and 20.7 (CH_3), 21.6 (CH_3-Ar); 28.1 (d, C-3); 47.4 (CH_2-CH=CH_2); 62.2 (C-1); 66.6 (C-2); 117.8 (CH=CH_2), 135.9 (CH=CH_2), Ar-C: 127.5, 129.6, 138.3, 143.3.

(S)-(+)-3-Benzyl-2.5-dimethyl-3-aza-5-hexen-1-ol (**5f**): A mixture of (S)-2-benzylamino-1-propanol (4.45 g, 27 mmol), 3-chloro-2-methyl-1-propene (2.5 g, 27 mmol) and potassium carbonate (7.45 g, 53.9 mmol) in

water was stirred at 62°C for 24 hours. Subsequently, the reaction mixture was extracted with diethyl ether. The etheral layer was dried over $MgSO_4$. From the crude product obtained after removal of the solvent, an excess of 3-chloro-2-methyl-1-propene was removed under vacuum at 60°C. **5f** was obtained as colourless oil in 92% yield (5.43 g) after distillation (kugelrohr, 120°C, 0.13 mbar). $[\alpha]_D^{19}$ = 39.6° - MS(FD): m/z (%) = 219 (100) [M^+]. - IR (neat): 3440, 3060 cm^{-1}. - ^1H NMR: δ = 0.85 (d, 3H, 2-CH_3); 1.71 (s, 3H, 5-CH_3); 2.84 (d, 1H, 4-H); 2.97 (m, 1H, 2-H); 3.08 (d, 1H, CH_2Ph); 3.22 (d, 1H, 4-H'); 3.35 (m, 2H, 1-H); 3.79 (d, 1H, CH_2Ph); 4.86 (s, 1H, 6-H); 4.92 (s, 1H, 6-H'); 7.24 (m, 5H, Ar-H). - J (2/CH_3) = 6.6, ^2J(4/4') = 13.6, ^2J(CH_2-Ph) = 13.4 Hz. - ^{13}C NMR: δ = 8.2 (2-CH_3), 20.6 (5-CH_3), 52.9 (CH_2Ph); 53.8 (C-2); 55.3 (C-4); 62.7 (C-1); 113.8 (C-6), 143.0 (*C*-5), Ar-C: 127.1; 128.4, 128.9, 139.3.

Ethyl (S)-(+)-5-benzyl-7-hydroxy-6-methyl-5-aza-2-heptenoate (**5g**): was prepared from (S)-2-benzylamino-1-propanol and ethyl 4-bromocrotonate as described for **5f**. Reaction time 48 h at 60°C. Removal of an excess of the bromocrotonate at 70°C under vacuum. Orange oil in 79% yield. $[\alpha]_D^{22}$ = 21.4° - $C_{16}H_{23}NO_3$ (277.4) Calcd. C 69.29 H 8.36 N 5.05 Found C 69.45 H 8.53 N 5.24. - MS (FD): m/z (%) = 555 (100) [2 M^+], 833 (77) [3 M^+]. - IR (neat): 3460, 3040, 1715 cm^{-1}. - ^1H NMR: δ = 0.88 (d, 3H, CH_3); 1.22 (t, 3H, CH_2-CH_3); 2.95 (m, 1H, 6-H); 3.07 (ddd, 1H, 4-H); 3.31 (ddd, 1H, 4-H'); 3.32 (d, 1H, CH_2Ph); 3.34 (m, 2H, 7-H and 7-H'); 3.75 (d, 1H, CH_2Ph); 4.12 (q, 2H, CH_2-CH_3); 5.91 (ddd, 1H, 2-H); 6.82 (ddd, 1H, 3-H); 7.23 (m, 5H, Ar-H). - J (2/3) = 15.9, J (3/4) = 7.7, J (3/4') = 4.7, J (6/CH_3) = 6.7, J(CH_2-CH_3) = 7.1, ^2J (4/4') = 15.6, ^2J(CH_2-Ph) = 13.5, ^4J (2/4) = 1.8, ^4J (2/4') = 1.2 Hz. - ^{13}C NMR: δ =9.3 (CH_3-CH_2), 14.2 (CH_3), 50.2 and 53.3 (C-4 and CH_2-Ph); 55.7 (C-6); 60.3 and 63.0 (C-7 and CH_2-CH_3); 123.0 (C-2), 146.2 (C-3), 166.0 (C-1), Ar-C: 127.3; 128.5, 128.7, 138.6.

Preparation of compounds **9**: Swern oxidation of compounds **5a-g** and subsequent reaction with N-alkylhydroxylamines or hydroxylamine, respectively, were performed as described.[3]

The following compounds **9A-B** were formed by spontaneous intramolecular cycloaddition of the intermediate nitrones 7: **9Aa**,[3] **Ab**,[3] **Ac**,[3] **Ad**, **Af**, **Ag**, **Ba**,[3] **Bc**,[3] **Be**, **Bf**.

(1R,5R,8S)-(+)-2-tert-Butyl-8-isopropyl-3-oxa-2,7-diazabicyclo[3.3.0]octane (**9Ad**): Brown oil (CC, Al_2O_3, ethyl acetate/diethyl ether 2:1, R_f = 0.43), 29% yield. $[\alpha]_D^{20}$ = 25.1° - MS (FD): m/z(%) = 212 (20) [M^+]. - IR (neat): 3319, 1668, 1387, 1060 cm^{-1}. - ^1H NMR see table 2. Additional data: δ = 0.86 (d, 3H, CH_3); 0.95 (d, 3H, CH_3); 1.06 (s, 9H, $C(CH_3)_3$); 1.67 (d sept, 1H, $CH(CH_3)_2$); 2.05 (s, 1H, NH). - J (8/$CH(CH_3)_2$) = 6.7, J($CH(CH_3)_2$) = 6.8, ^2J (4α/4β) = 7.7, ^2J (6α/6β) = 7.6 Hz. - ^{13}C NMR: δ = 17.8 (CH_3), 21.2 (CH_3), 26.7 ($C(CH_3)_3$) 29.0 ($CH(CH_3)_2$); 50.6 (C-5); 51.7 (C-6), 59.0 ($C(CH_3)_2$); 68.8 (C-1);71.2 (C-8); 73.8 (C-4).

(1R,5R,8S)-(+)-7-Benzyl-2-tert-butyl-5,8-dimethyl-3-oxa-2.7-diazabicyclo[3.3.0]octane (**9Af**): Yellow oil (CC, Al_2O_3, diethyl ether R_f = 0.50), 55% yield. $[\alpha]_D^{21}$ = 49.2° - MS (FD): m/z (%) = 288 (100) [M^+] - ^1H NMR see table 2. Additional data: δ = 1.08 (d, 9H, $C(CH_3)_3$); 1.08 (d, 3H, CH_3); 1.20 (s, 3H, CH_3); 3.33 (d, 1H, CH_2Ph); 3.79 (d, 1H, CH_2Ph); 7.23 (m, 5H, Ar-H). - J (8/CH_3) = 6.4, ^2J (4α/4β) = 8.0, ^2J (6α/6β) = 8.9, ^2J (CH_2Ph) = 13.3 Hz.

(1R,4R,5R,8S)-(+)-7-Benzyl-2-tert-butyl-4-ethoxycarbonyl-8-methyl-3-oxa-2.7-diazabicyclo[3.3.0]-octane (**9Ag**): Brown oil in 61% yield. $[\alpha]_D^{22}$ = 13.7° - MS (FD): m/z (%) = 346 (100) [M^+], 692 (63) [$2M^+$]. - IR (neat): 1740, 1450, 1190, 940 cm^{-1}. - ^1H NMR see table 2. Additional data: δ = 1.09 (d, 3H, CH_3); 1.11 (s, 9H, $C(CH_3)_3$); 1.21 (t, 3H, CH_2CH_3); 3.41 (d, 1H, CH_2Ph); 3.87 (d, 1H, CH_2Ph); 4.14 (q, 2H, CH_2-CH_3); 7.26 (m,5H, Ar-H). - *J* (8/CH_3) = 6.3, *J* (CH_2-CH_3) = 5.2, ^2J (6α/6β) = 8.8, ^2J (CH_2Ph)= 13.2 Hz. - ^{13}C NMR: δ = 14.0 (CH_3), 14.4 (CH_3), 25.9 ($C(CH_3)_3$) 50.6 (C-5);); 55.1 (CH_2CH_3); 56.1 (CH_2Ph), 58.7 ($C(CH_3)_3$); 60.9 (C-6); 63.2 (C-8); 71.6 (C-1), 82.2 (C-4), 170.6 (C=O); ArC: 126.8, 128.1, 128.5, 138.8.

(1R,5R,8S)-(+)-2-Benzyl-8-isoproyl-7-tosyl-3-oxa-2.7-diazabicyclo[3.3.0]octane (**9Be**): Colourless solid, m.p. 82°C (CC, Al_2O_3, diethyl ether, R_f = 0.43) 50 % yield. $[\alpha]_D^{23}$ = 5.8°. - $C_{22}H_{28}N_2O_3S$ (400.5) Calcd. C 65.97 H 7.05 N 6.99 Found C 66.44 H 7.41 N 6.71. - MS (FD): m/z (%) = 400 (100) [M^+]. - IR (KBr): 1261, 1089, 1017, 800 cm^{-1}. ^1H NMR (500 MHz) see table 2. Additional data: δ = 0.86 (d, 3H, CH_3); 0.90 (d, 3H, CH_3); 2.23 (m, 1H, $CH(CH_3)_2$); 2.41 (s, 3H, Ar-CH_3); 3.72 (d, 1H, CH_2Ph); 3.80 (d, 1H, CH_2Ph); 7.17 (d, 2H, Ar-H); 7.27 (m, 5H, Ar-H); 7.77 (d, 2H, Ar-H). - *J* (8/$CH(CH_3)_2$) = 5.1, *J* ($CH(CH_3)_2$) = 7.0, ^2J (4α/4β) = 11.2, ^2J (6α/6β) = 8.2, ^2J (CH_2Ph)= 13.6 Hz. - ^{13}C NMR: δ = 16.9 (CH_3), 19.2 (CH_3), 21.4 (Ar-CH_3), 32.0 ($CH(CH_3)_2$); 46.9 (C-5), 52.7 (C-4), 60.3 (CH_2Ph), 69.7 (C-8), 71.1 (C-6); 72.4 (C-1); Ar-C: 127.3, 127.7, 128.1, 128.6, 135.4, 136.8, 143.2.

(1R,5R,8S)-(+)-2.7-Dibenzyl-5.8-dimethyl-3-oxa-2.7-diazabicyclo[3.3.0]octane (**9Bf**): Yellow oil (CC, Al_2O_3, diethyl ether R_f = 0.80), 58% yield. $[\alpha]_D^{21}$ = 74.2°. - MS (FD): m/z (%) = 322 (100) [M^+], 645 (56) [$2M^+$]. - IR (neat): 1450, 1380, 1030, 740 cm^{-1}. - ^1H NMR see table 2. Additional data: δ = 1.00 (d, 3H, CH_3); 1.39 (s, 3H, CH_3); 3.07 (d, 1H, CH_2Ph); 3.88 (d, 1H, CH_2Ph); 3.95 (d, 1H, CH_2Ph); 4.20 (d, 1H, CH_2Ph); 7.32 (m, 10H, Ar-H). - *J* (8/CH_3) = 6.2, ^2J (4α/4β) = 8.8, ^2J 6α/6β = 8.8, ^2J (CH_2Ph)= 12.4, ^2J (CH_2Ph)= 13.2 Hz. - ^{13}C NMR: δ = 17.0 (CH_3), 25.2 (CH_3), 53.7 (C-5), 57.1 (CH_2Ph), 60.1 (C-6); 65.9 (CH_2Ph), 66.2 (C-8), 73.3 (C-4); 84.1 (C-1); Ar-C: 126.8, 127.5, 128.2, 128.4, 128.6, 129.4, 137.1.

Preparation of oximes **8**: Swern oxidation of **5a** and **b** and subsequent reaction of aldehydes **6a** and **b** with hydroxylamine afforded the oximes **8a** and **b**, respectively.

(S)-2-(N-Allyl-benzylamino)-3-methylbutanal oxime (**8b**): Colourless oil, 1:4 mixture of syn- and anti-product, 77% yield. - ^1H NMR (syn/anti): δ = 0.87/0.98 (d, 3H, CH_3); 1.09/1.11 (d, 3H, CH_3); 1.92/1.98 (m, 1H, $CH(CH_3)_2$); 2.87 (dd, 1H, $(CH_3)_2CH$-CH); 3.01 (dd, 1H, CH_2-CH=CH_2); 3.38 (ddt, 1H, CH_2'-CH=CH_2); 3.71/3.45 (d, 1H, CH_2Ph); 3.97/3.92 (d, 1H, CH_2Ph); 5.20 (m, 2H, CH=CH_2); 5.83 (m, 1H, CH=CH_2); 6.73/7.45 (d, 1H, N=CH); 7.33 (m, 10H, Ar-H). - *J*(N=CH-CH) = 7.2/9.0, *J* (CH-$CH(CH_3)_2$) = 10.2, *J* ($CH(CH_3)_2$) = 6.6/6.8, *J* (CH_2-CH=CH_2) = 8.1, *J* (CH_2'-CH=CH_2) = 4.0, ^2J(CH_2-CH=CH_2) = 14.2, ^2J(CH_2Ph) = 14.6/13.9, ^4J(CH_2'-CH=CH_2) = 2.1 Hz. - ^{13}C NMR (anti): δ =19.9 (CH_3), 20.1 (CH_3), 28.3 ($CH(CH_3)_2$); 52.7 (CH_2Ph); 53.9 (CH_2-CH=CH_2); 64.2 (CH_2-CH=CH_2); 117.0 (CH=CH_2), 136.7 (CH=CH_2); 150.7 (N=CH), ArC: 126.7-129.0, 140.0 or 139.9.

Additional signals of the syn isomer: δ = 31.5, 117.3, 137.0, 152.3, Ar-C 139.9 or 140.0.

Oximes **8a** and **b** were converted to compounds **9Ca**[3] and **Cb**, respectively, by heating in toluene (10 mmol in 50 mL) for eight h.

(1R,5R,8S)-(+)-7-Benzyl-8-isopropyl-3-oxa-2.7-diazabicyclo[3.3.0]octane (**9Cb**): Colourless needles, m.p. 139°C (diethyl ether), 64% yield. $[\alpha]_D^{22}$ = 5.3°. - $C_{15}H_{22}N_2O$ (246.4) Calcd. C 73.13 H 9.00 N 11.37 Found C 72.66 H 9.19 N 11.28. - MS (FD): m/z (%) = 246 (100) [M^+]. - IR (KBr): 3172, 2961, 1454, 697 cm^{-1}. - ^1H NMR see table 2. Additional data: δ = 1.00 (d, 3H, CH_3); 1.07 (d, 3H, CH_3); 2.18 (m, 1H, C*H*(CH_3)$_2$); 2.99 (d, 1H, CH_2Ph); 4.01 (d, 1H, CH_2Ph); 5.11 (s, 1H, NH); 7.27 (m, 5H, Ar-H). - *J* (C*H*(CH_3)$_2$) = 6.6, *J* (8/C*H*(CH_3)$_2$) not detectable, ^2J (4α/4β) = 8.7, ^2J (6α/6β) = 8.7, ^2J (C*H*$_2$Ph)= 12.8 Hz. - ^{13}C NMR: δ = 15.5 (CH_3), 19.7 (CH_3), 26.5 (*C*H(CH_3)$_2$), 46.0 (C-5), 57.2 (CH_2Ph), 58.9 (C-6), 65.4 (C-1); 73.9 (C-8), 75.6 (C-4); Ar-C: 126.7, 128.1, 128.6, 139.1.

(1R,4R,5R,8S)-(+)-7-Benzyl-2-tert-butyl-4-hydroxymethyl-8-methyl-3-oxa-2.7-diazabicyclo[3.3.0]-octane (**9Ah**): A solution of **9Ag** (1.21 g, 3.5 mmol) in 10 mL of diethyl ether was dropped to a suspension of lithium aluminum hydride (0.13 g, 3.5 mmol) in 10 mL of diethyl ether at 0°C under nitrogen. After stirring the reaction mixture for two h at room temperature water (2 mL), NaOH (15%, 2 mL) and again water (5 mL) were added successively, followed by extraction with diethyl ether. The etheral layer was dried over magnesium sulfate. Removal of the ether afforded **9Ah** as a colourless solid, m.p. 94°C (CC, Al_2O_3, diethyel ether, R_f = 0.55) in 59% yield (0.63 g). $[\alpha]_D^{22}$ = 39.3°. - MS (FD): m/z (%) = 304 (100) [M^+]. - IR (KBr): 3251, 1362, 1094, 743 cm^{-1}. - ^1H NMR see table 2. Additional data: δ = 1.02 (d, 3H, CH_3); 1.07 (s, 9H, C(CH_3)$_3$); 1.67 (s, 1H, OH); 3.48 (d, 1H, CH_2Ph); 3.52 (dd, 1H, C*H*$_2$OH); 3.75 (dd, 1H, C*H*$_2$'OH);); 3.75 (d, 1H, CH_2Ph); 7.24 (m, 5H, Ar-H). - *J* 8/CH_3) = 6.5, *J* (4/CH_2OH) = 4.8, *J* (4/CH_2'OH) = 3.3, ^2J (6α/6β) = 9.1, ^2J(C*H*$_2$OH)= 13.1, ^2J (CH_2Ph) = 13.2 Hz. - ^{13}C NMR: δ = 13.6 (CH_3), 25.9 (C(*C*H$_3$)), 47.4 (C-5), 53.2 (C-6), 56.0 (CH_2Ph), 58.4 (*C*(CH_3)$_3$), 62.4 (CH_2OH); 63.6 (C-8), 72.0 (C-1), 83.1 (C-4); Ar-C: 126.9, 128.3, 128.7, 139.2.

(1R,5R,8S)-(+)-7-Allyl-8-isopropyl-2-tosyl-3-oxa-2.7-diazabicyclo[3.3.0]octane (**9Da**): Potassium carbonate (1.41 g, 10 mmol) and tosyl chloride (0.97 g, 5.1 mmol) were added successively to a solution of 1.0 g (5.1 mmol) of **9Ca** in 50 mL of dichloromethane. The reaction mixture was refluxed for three h and then stirred at room temperature for 24 h. After the organic layer had been washed with water and dried over magnesium sulfate the solvent was removed. Yellow oil, 76% yield. $[\alpha]_D^{22}$ = 139.2°. - $C_{18}H_{26}N_2O_3S$ (350.5) Calcd. C 61.69 H 7.48 N 7.99 Found C 61.92 H 7.77 N 8.04. - MS (FD): m/z (%) = 350 (100 [M^+]. - IR (neat): 3080, 1610, 1175, 935 cm^{-1}. ^1H NMR see table 2. Additional data: δ = 0.94 (d, 3H, CH_3); 1.12 (d, 3H, CH_3); 2.03 (m, 1H, C*H*(CH_3)$_2$); 2.37 (s, 3H, Ar-CH_3); 2.58 (dd, 1H, C*H*$_2$-CH=CH_2); 3.34 (dd, 1H, C*H*$_2$'-CH=CH_2); 5.08 (m, 2H, CH=C*H*$_2$); 5.76 (m, 1H, C*H*=CH_2); 7.27 (d, 2H, Ar-H); 7.77 (d, 2H, Ar-H). - *J* (8/C*H*(CH_3)$_2$) = 3.4, *J* (C*H*(CH_3)$_2$) = 6.8, *J*(C*H*$_2$-C*H*=CH_2)= 7.9, *J* (C*H*$_2$'-C*H*=CH_2) = 5.2 ^2J (4α/4β) = 8.2, ^2J (6α/6β) = 9.0, ^2J (C*H*$_2$-CH=CH_2) = 13.5 Hz - ^{13}C NMR: δ = 15.5 (CH_3), 19.1 (CH_3), 21.7 (Ar-CH_3), 26.9 (*C*H(CH_3)$_2$), 45.3 (C-5), 55.5 (*C*H$_2$-CH=CH_2), 59.1 (C-6), 63.3 (C-8), 73.5 (C-1), 74.8 (C-4), 117.3 (CH=C*H*$_2$), 135.0 (*C*H=CH_2); Ar-C: 129.0, 129.7, 134.0, 144.9.

Bis[(1R,5R,8S)-(+)-7-Benzyl-8-isoproyl-3-oxa-2.7-diazabicyclo[3.3.0]octane-2]1.2-ethane (**10**): 0.740 g (3.0 mmol) of **9Cb** in 50 mL of dichloromethane were mixed with 0.83 g (6.0 mmol) of potassium carbonate. After addition of 0.139 g (1.1 mmol) of oxalyl chloride the reaction mixture was stirred for 12 h at room

temperature. The organic layer was washed with water and dried over magnesium sulfate. Then the solvent was removed affording the corresponding ethane dione as yellow crystals (m.p. 170°). This compound was reduced according to the procedure of Giannis and Sandhoff[5] as follows: A suspension of 0.17 g (4 mmol) of lithium chloride and 0.215 g (4 mmol) of potassium borohydride in 5 mL tetrahydrofuran was stirred for 20 h under nitrogen. Then 0.865 g (8 mmol) of trimethylsilyl chloride and the ethane dione (0.546 g, 1 mmol) were successively added. After stirring for 24 h 5 mL of methanol were added. The reaction mixture was evaporated to dryness. The residue was treated with 5 mL of a solution of potassium hydroxide (20%) and extracted with dichloromethane. The organic layer was dried over magnesium sulfate. After removal of the solvent and recrystallization from petroleum ether colourless crystals were obtained. M.p. 79°C, 32% yield. $[\alpha]_D^{22}$ = 121.9°. - MS (FD): m/z (%) = 519 (100) [M^+]. - IR (KBr): 2962, 1261, 801 cm^{-1}. ^{1}H-NMR: δ = 0.93 (d, 6H, CH_3); 0.99 (d, 6H, CH_3); 1.90 (dd, 2H, 6-H); 2.08 (m, 2H, CH_2-CH_2); 2.13 (m, 2H, CH(CH_3)$_2$); 2.24 (dd, 2H, 8-H); 2.74 (m, 2H, CH_2- CH_2); 2.94 (m, 2H, 5-H); 2.95 (d, 2H, CH_2Ph); 3.06 (dd, 2H, 6-H'); 3.29 (dd, 2H, 4-H); 3.49 (d, 2H, 4-H'); 3.83 (dd, 2H, 1-H); 3.94 (d, 2H, CH_2Ph); 7.20 (m, 10H, Ar-H). - *J* (1/5) = 8.9, *J* (1/8) = 6.5, *J* (4/5) = 6.7, *J* (4'/5) <1, *J* (5/6) = 8.8, *J* (5/6') = 8.5, *J* (8/CH(CH_3)$_2$) = 3.8, *J* (CH(CH_3)$_2$) = 6.8, ^{2}*J* (4/4') = 8.8, *J* (6/6') = 8.8, ^{2}*J* (CH_2-Ph) = 12.9 Hz. - ^{13}C NMR: δ = 15.9 (CH_3), 19.8 (CH_3), 27.1 (*C*H(CH_3)$_2$), 45.5 (C-5), 54.0 (*C*H_2-CH_2), 57.6 (*C*H_2Ph), 59.3 (C-6), 68.4 (C-4), 72.7 (C-8), 73.5 (C-1); Ar-C: 126.8, 128.2, 128.6, 139.4.

Bis[(1R,5R,8S)-(+)-2-tert-butyl-8-isopropyl-3-oxa-2.7-diazabicyclo[3.3.0]octane-7]ethane (**11**): Oxalyl chloride (0.16 mL, 1.91 mmol) was added to a suspension of **9Ad** (0.81 g, 3.82 mmol) and potassium carbonate (1.58 g, 11.5 mmol) in dichloromethane (50 mL). The reaction mixture was stirred for 12 h at room temp. Then it was treated with water (50 mL). The organic layer was subsequently dried with $MgSO_4$. After removal of the solvent the resulting diamide was separated by chromatography (ethyl acetate/diethyl ether 1:3, R_f = 0.55, 0.34 g, 38% yield). Then the diamide was dissolved in THF (0.22 g, 0.46 mmol in 20 mL) under nitrogen. This solution was dropped to a suspension of lithium aluminum hydride (35 mg, 0.92 mmol) in THF (50 mL). The reaction mixture was refluxed for 12 h. After removal of the THF the residue was treated with diethyl ether and hydrolysed by successive addition of water (10 mL) and NaOH (15%, 10 mL). The insoluble salts were separated by filtration. The organic layer was dried with $MgSO_4$. Removal of the solvent afforded a light-yellow oil (0.121 g) in 22% total yield. -MS (FD): m/z (%) = 450 (100) [M^+]. - IR (neat): 1465, 1362, 1214, 1057 cm^{-1}. - ^{1}H NMR: δ = 0.95 (d, 6H, CH_3); 0.98 (d, 6H, CH_3); 1.05 (s, 18H, C(CH_3)$_3$); 1.92 (m, 2H, CH(CH_3)$_2$); 2.08 (dd, 2H, 6-H); 2.18 (dd, 2H, 8-H); 2.24 (m, 2H, N-CH_2-CH_2-N); 2.86 (m, 2H, N-CH_2-CH_2-N); 2.99 (m, 2H, 5-H); 3.38 (dd, 2H, 6-H'); 3.54 (dd, 2H, 1-H); 3.55 (dd, 2H, 4-H); 3.94 (dd, 2H, 4-H'). - *J* (1/5) = 6.6, *J* (1/8) = 6.8, *J* (4/5) = <1, *J* (4'/5) = 7.6, *J* (5/6) = 7.7, *J* (5/6') = 8.7, *J* (8/CH) = 2.2, *J* (CH(CH_3)$_2$) = 7.4, ^{2}*J* (4/4') = 7.6, ^{2}*J* (6/6') = 8.7 Hz. - ^{13}C NMR: δ = 17.6 (CH_3); 19.7 (CH_3); 27.5 (C(*C*H_3)$_3$); 28.4 (CH(*C*H_3)$_2$); 47.3 (C-5), 53.5 (N-$CH_2$$CH_2$-N), 59.9 (*C*($CH_3$)$_3$); 60.4 (C-6); 67.3 (C-1; 74.6 (C-8); 74.7 (C-4).

(2S,3R,4R)-(+)-1-Benzyl-3-tert-butylamino-4-hydroxymethyl-2-methylpyrrolidine (**12Ac**): The reduction of **9Ac** affording **12Ac** was performed as described before for the reduction of **9Aa**.[3] 74% yield, colourless crystals from petroleum ether, m.p. 82°C. $[\alpha]_D^{21}$ = 64.4°. $C_{17}H_{28}N_2O$ (276.4) Calcd. C 73.87 H 10.21 N 10.13 Found C 73.91 H 10.50 N 9.97. - MS (FD) m/z (%) = 276 (94) [M^+], 277 (100) [M^++1]. - IR (KBr): 3300 cm^{-1}. ^{1}H NMR (500 MHz): δ = 1.13 (s, 9H, C(CH_3)$_3$); 1.19 (d, 3H, CH_3); 2.17 (m, 1H, 4-H); 2.17 (dd, 1H, 5-H); 2.32 (dq, 1H, 2-H); 2.95 (dd, 1H, 5-H'); 3.09 (dd, 1H, 3-H); 3.19 (d, 1H, CH_2Ph); 3.59 (dd, 1H, C*H*OH); 3.70

(dd, 1H, C*H*'OH); 3.93 (s, 2H, OH and NH); 3.99 (d, 1H, CH_2'Ph); 7.25 (m, 5H, Ar-H). - *J* (2/CH_3) = 6.1, *J* (2/3) = 7.8, *J* (3/4) = 7.8, *J* (4/C*H*OH) = 6.4, *J* (4/C*H*'OH) = 3.4, *J* (4/5) = 5.6, *J* (4'/5) = 10.7, ^2J (CH_2Ph) = 12.9, ^2J (CH_2OH) = 11.7 Hz. - ^{13}C NMR: δ = 16.7 (CH_3), 29.7 (C(CH_3)$_3$), 39.8 (C-4), 51.4 (s, *C*(CH_3)$_3$), 54.6 (C-5), 58.3 (CH_2Ph), 62.0 (C-3), 63.9 (CH_2OH), 64.6 (C-2), ArC: 126.9, 128.2, 128.9, 139.1.

(2S,3R,4R)-(+)-N-(1-Allyl-4-hydroxymethyl-2-isopropylpyrrolidine-3)-4-toluene sulfonamide (**12Da**): Reduction of **9Da** as described earlier for reduction of **9Aa**[3] afforded a yellow oil in 61% yield (CC, acetone, R_f = 0.68). $[\alpha]_D^{22}$ = 25.4°. - MS (FD): m/z (%) = 352 (100) [M^+]. - IR (neat): 3500, 3280, 3080, 1165 cm^{-1}. - ^{1}H NMR: δ = 0.53 (d, 3H, CH_3), 0.55 (d, 3H, CH_3), 1.43 (m, 1H, C*H*(CH_3)$_2$); 2.08 (dd, 1H, 2-H); 2.22 (m, 1H, 4-H); 2.37 (s, 3H, Ar-CH_3); 2.91 (dd, 1H, CH_2-CH=CH_2); 2.92 (dd, 1H, 5-H); 3.27 (dd, CH_2'-CH=CH_2); 3.51 (dd, 2H, C*H*OH and 5-H'); 3.78 (dd, 1H, C*H*'OH); 5.08 (m, 2H, CH=CH_2); 5.15 (dd, 1H, 3-H); 5.75 (m, 1H, C*H*=CH_2); 7.26 (d, 2H, Ar-H); 7.73 (d, 2H, Ar-H). - *J* (2/C*H*(CH_3)$_2$) = 2.6, *J* (2/3) = 5.6, *J* (3/4) = 8.2, *J* (4/C*H*OH) = 3.5, *J* (4/C*H*'OH) = 7.4, *J* (4/5) = 5.8, *J* (4/5') not detectable, *J* (C*H*(CH_3)$_2$) = 4.8, *J* (C*H*-C*H*=CH_2) = 7.9, *J* (C*H*'-C*H*=CH_2) = 5.3, ^2J (5/5') = 7.6, ^2J (CH_2OH) = 11.7 ^2J (CH_2-CH=CH_2) = 13.6 Hz. - ^{13}C NMR: δ = 18.1 (CH_3), 18.7 (CH_3), 21.4 (Ar-CH_3), 30.8 (*C*H(CH_3)$_2$), 43.6 (C-4), 53.0 (C-5), 56.3 (C-2), 58.2 (*C*H_2-CH=CH_2), 59.8 (CH_2OH), 77.2 (C-3), 117.0 (CH=*C*H_2), 135.3 (*C*H=CH_2), ArC: 127.2, 129.6, 137.4, 143.6.

(1R,4R,5R,8S)-(+)-7-Benzyl-2-tert-butyl-4-hydroxy-8-methyl-2.7-diazabicyclo[3.3.0]octanone-3 (**13**): Compound **9Ag** was reduced with zinc in acetic acid at 65°C for 3 d as described for the reduction of **9Aa**.[3] **13** was obtained in 62% yield, colourless crystals, m.p. 38°C (diethyl ether/petroleum ether 1:2). $[\alpha]_D^{22}$ = 31.1°. - MS (FD): m/z (%) = 302 (100) [M^+]. - IR (KBr): 3350, 1680, 1370, 1160 cm^{-1}. - ^{1}H NMR: δ = 0.96 (d, 3H, CH_3); 1.32 (s, 9H, C(CH_3)$_3$); 2.60 (dd, 1H, 6-H); 2.77 (m, 1H, 5-H); 2.94 (dd, 1H, 6-H'); 3.05 (dq, 1H, 8-H); 3.49 (d, 1H, CH_2Ph); 3.69 (d, 1H, CH_2'Ph); 3.77 (dd, 1H, 1-H); 4.01 (d, 1H, 4-H); 4.76 (s, 1H, OH); 7.18 (m, 5H, Ar-H). - *J* (1/5) = 7.4, *J* (1/8) = 0.9, *J* (4/5) = 9.2, *J* (5/6) = 6.5, *J* (5/6') = 3.1, *J* (8/CH_3) = 6.6, ^2J (6/6') = 9.7, ^2J (CH_2Ph) = 13.2 Hz. - ^{13}C NMR: δ = 10.4 (CH_3), 27.1 (C(*C*H_3)$_3$), 36.5 (C-5), 47.6 (C-6), 53.7 (CH_2Ph), 53.7 (*C*(CH_3)$_3$), 60.8 (C-8), 66.6 (C-1), 69.5 (C-4), 173.7 (C-3), Ar-C: 126.1, 127.3, 127.4, 137.4.

(1R,4R,5R,8S)-(+)-7-Benzyl-2-tert-butyl-4-hydroxy-8-methyl-2.7-diazabicyclo[3.3.0]octane (**14**): The reduction of **13** was performed according to the procedure of Giannis and Sandhoff[5] as described for the formation of **10**. Thus, **14** was obtained as colourless oil (CC, diethyl ether, R_f = 0.62) in 54% yield. $[\alpha]_D^{21}$ = 20.3°. - MS (FD): m/z (%) = 288 (100) [M^+]. - IR (neat): 3390, 1470, 1385, 710 cm^{-1}. - ^{1}H NMR (500 MHz): δ = 0.87 (d, 3H, CH_3); 0.97 (s, 9H, C(CH_3)$_3$); 2.46 (dd, 1H, 6α-H); 2.48 (m, 1H, 5-H); 2.50 dd, 1H, 3α-H); 2.81 (d, 1H, 6β-H); 2.90 (d, 1H, 3β-H); 2.94 (d, 1H, 1-H); 3.02 (q, 1H, 8-H); 3.47 (d, 1H, CH_2Ph); 3.64 (d, 1H, CH_2Ph); 3.94 (dd, 1H, 4-H); 7.23 (m, 5H, Ar-H). - *J* (1/5) = 8.9, *J* (1/8) = <1, *J* (3α/4) = 3.0, *J* (3β/4) = <1, *J* (4/5) = 5.5, *J* (5/6α) = 5.7, *J* (5/6β) = <1, *J* (8/CH_3) = 6.8, ^2J (3α/3β) = 9.6, ^2J (6α/6β) = 9.2, ^2J (CH_2Ph) = 13.0 Hz.- ^{13}C NMR: δ = 10.1 (CH_3), 26.8 (C(*C*H_3)$_3$), 45.7 (C-5), 49.1 (C-6), 53.0 (*C*(CH_3)$_3$), 54.4 (CH_2Ph), 57.6 (C-3), 64.8 (C-8), 68.9 (C-1), 72.5 (C-4), Ar-C: 127.2, 128.5, 128.6, 138.7.

Catalysis of the reaction of diethylzinc with benzaldehyde. Freshly distilled benzaldehyde (0.25 mL, 2.5 mmol) was added to the catalyst (0.15 mmol of compounds **9, 10, 11, 12** or **14**) in a 10 mL flask under argon.

The clear solution was cooled to 0°C, then a 1.0 M solution of diethylzinc in hexane (3.75 mL, 3.75 mmol) was added within a period of 20 min. Alternatively, in a few cases a 1.1 M solution in toluene (3.4 mL, 3.75 mmol) was used. The reaction mixture was stirred for 12 h, then the reaction was quenched with 1.5 M hydrochloric acid (10 mL). Subsequently the mixture was extracted three times with diethyl ether. The combined organic layer was dried with $MgSO_4$. After filtration and removal of the solvent a non-racemic mixture of (*R*)- and (*S*)-1-phenyl-1-propanol **15** was obtained in more then 90% yield. ^{1}H NMR: δ = 0.90 (t, 3H, 3-H); 1.66-189 (m, 2H, 2-H); 2.01 (s, 1H, OH); 4.58 (dd, 1H, 1-H); 7.23-7.25 (m, 5H, Ar-H). - *J* (1/2) = 6.7, *J* (1/2') = 6.5, *J* (2/3) = 7.4 Hz. - ^{13}C NMR: δ = 10.1 (C-3), 31.8 (C-2), 76.0 (C-1), Ar-C: 125.9, 127.4, 128.3, 144.6.

Determination of the enantiomeric excess of 1-phenyl-1-propanol (15) with the aid of the diastereomeric esters 16 obtained by reaction with (S)-(+)-O-acetyl mandelic acid..

1-Phenyl-1-propanol (**15**) (94.3 mg, 0.69 mmol) was dissolved in dichloromethane (10 mL) under nitrogen. The solution was cooled to -10°C. Successively 4-N.N-dimethylamino pyridine (5 mg), (S)-(+)-O-acetyl mandelic acid (134 mg, 0.69 mmol) and dicyclohexyl carbodiimide (143 mg, 0.69 mmol) were added. The reaction mixture was stirred for 2 h at -10°C and additional 12 h at -26°C. Then the solution was separated from the precipitate and the solvent removed by distillation. *2.5-Dioxo-4.7-diphenyl-3.6-dioxa-nonane* (**16**): MS (EI): m/z (%) = 312(13) [M^+]. - ^{1}H NMR: (R.S)-**16**, the signals of the diastereomer (S.S)-**16** are given in brackets. The triplets at 0.63 and 0.88 ppm from which the diasteromeric excess was determined are separated by 72.6 Hz: δ 0.63 [0.88] (t, 3H, CH_2CH_3); 1.64-1.85 (m, 2H, CH_2CH_3), 2.16 [2.18] (s, 3H, CH_3CO_2); 5.66 [5.65] (dd, 1H, OC*H*-CH_2-CH_3); 5.97 [5.98] (s, 1H, PhCH-CO_2); 6.94-7.50 (m, 10H, Ar-H). - *J* (CH_2-CH_3) = 7.4, *J* (OC*H*(Ph)-C*H*-CH_3) = 7.4, *J* (OC*H*(Ph)-CH'-CH_3) = 6.0 Hz. - ^{13}C NMR: δ = 9.3 [9.6] (CH_2CH_3), 20.6 (CH_3CO_2), 29.0 [29.2] (CH_2-CH_3), 74.5 (O$CHCH_2CH_3$), 78.6 [78.7] (Ph$CHCO_2$), 168.2 [168.0] and 170.0 [170.2] (C=O), Ar-C: 126.0-139.6.

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References

1. a) Tufariello, J.J. in *1.3 Dipolar Cycloaddition Chemistry*, Padwa, A. (Ed.) Chapter 9, Wiley - Interscience New York, **1984**, pp. 116-122; b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Gazz. Chim. Ital.* **1989**, *119*, 253-269, see pp. 266-268; c) Wade, P.A. In *Comprehensive Organic Synthesis*, Trost, B.M.; Fleming, I.; Semmelhack, M.E. (Eds.); Pergamon Press, Oxford **1991**, Vol. 4, pp. 1113-1114.
2. a) Baggiolini, E.G.; Lee, H.L.; Pizzolato, G.; Uskokovic, M.R. *J. Am. Chem. Soc.* **1982**, *104*, 6460-6462; b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Giaroni, P.; Raimondi, L. *Tetrahedron Asymmetry* **1990**, *1*, 251-264; c) Aurich, H.G.; Biesemeier, F.; Boutahar, M. *Chem. Ber.* **1991**, *124*, 2329-2334; d) Wovkulich, P.M.; Baggiolini, E.G.; Hennessy, B.M.; Uskokovic, M.R.; *Heterocycles* **1993**, *35*, 791-806; e) Rong, J.; Roselt, P.; Plavec, J.; Chattopadhyaya, J.. *Tetrahedron* **1994**, *50*, 4921-4936; f) Chiacchio, U.; Casuscelli, F.; Corsaro, A.; Librando, V.; Rescifina, A.; Romeo, R.; Romeo G. *Tetrahedron* **1995**, *51*, 5689-5700.
3. Aurich, H.G.; Frenzen, G.; Gentes, C. *Chem. Ber.* **1993**, *126*, 787-795.

4. See for instance: a) Soai, K.; Niwa, S.; *Chem. Rev.* **1992**, *92*, 833-856; b) Blaser, H.-U.; *Chem. Rev.* **1992**, *92*, 935-952; c) Noyori, R.; Kitamura, M.; *Angew. Chem.* **1991**, *103*, 34-55; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49; d) Tomioka; K; *Synthesis* **1990**, 541-549; e) Berrisford, D.J. *Angew. Chem.* **1995**, *107*, 192-194, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 178-180; f) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyma, T., *Tetrahedron* **1993**, *49*, 1761-1772; g) Kobayashi, S.; Horibe, M. *J. Am. Chem. Soc.* **1994**, *116*, 9805-9806; h) Nakajima, M.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *49*, 9751-9758; i) Nakajima, M.; Tomioka, K.; Iitaka, Y.; Koga, K. *Tetrahedron* **1993**, *49*, 10793-10806; j) Rossiter, B.E.; Eguchi, M.; Miao, G.; Swingle, N.M.; Hernandez, A.E.; Vickers, D.; Fluckiger, E.; Patterson, R.G.; Reddy, K.V. *Tetrahedron* **1993**, *49*, 965-986; k) Corey, E.J.; Sarshar, S.; Lee, D.-H. *J. Am. Chem. Soc.* **1994**, *116*, 1289-1290; l) Corey, E.J.; *Pure and Appl. Chem.* **1990**, *62*, 1209-1216; m) Falorni, M.; Giacomelli, G.; Marchetti, M.; Culeddu, N.; Lardicci, L. *Tetrahedron Asymmetry* **1991**, *2*, 287-298.
5. Giannis, A.; Sandhoff, K. *Angew. Chem.* **1989**, *101*, 220-222; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 218-220.
6. Quitt, P.; Hellerbach, J.; Vogler, K. *Helv. Chim. Acta* **1963**, *46*, 327-333.
7. a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651-1660; b) Marx, M.; Tidwell, T.T. *J. Org. Chem.* **1984**, *49*, 788-793.
8. a) Hassner, A.; Maurya, R.; Mesko, E. *Tetrahedron Lett.* **1988**, *29*, 5313-5316; b) Hassner, A.; Maurya, R.; Padwa, A.; Bullock, W.H. *J. Org. Chem.* **1991**, *56*, 2775-2781.
9. Parker, D.; Taylor, R.J. *Tetrahedron* **1987**, *43*, 5451-5456.
10. a) Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543-2549; b) Dale, J.A..; Mosher, H.S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519; c) In the ^{1}H NMR spectrum of the product some signals were assigned incorrectly (ref. 3). The correct assignment is as follows: δ = 2.14 (dd, 1H, 1-H); 3.09 (dd, 1H, 6-H'); 3.18 (dd, 1H, 4-H); 3.32 (dd, 1H, C*H*$_2$CH=CH$_2$); 4.71 (dd, 1H, 4-H').
11. The atomic coordinates and additional data such as bond lengths and angles for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW. Any request should be accompanied by the full literature citation for this communication.
12. Hesse, M.; Meier, H.; Zeeh, B. *Spektroskopische Methoden in der organischen Chemie*, Georg Thieme Verlag Stuttgart, **1991**, p. 105.
13. Similar results were obtained for a number of 3-oxa-2.7-diazabicyclo[3.3.0]octanes unsubstituted at N-2: Hassner, A.; Maurya, R.; Friedman, O.; Gottlieb, H.E.; Padwa, A.; Austin D. *J Org. Chem.* **1993**, *58*, 4539-4546.
14. The same phenomenon is observed for 4-hydroxy-4-methyl substituted 3-oxa-2.7-diaza-bicyclo[3.3.0]octanes: Aurich, H.G.; Köster, H. *Tetrahedron* **1995**, *51*, 6282-6292.
15. Takeuchi, Y.; Furusaki, F. in *Advances in Heterocyclic Chemistry*, E. Katritzky, A.R.; Boulton, A.J., (Eds.) Academic Press, New York, **1977**, Vol. 21, 207-251, see pp 243-244.
16. Le Bel, N.A.;Post, M.E.; Whang, J.J. *J. Am. Chem. Soc.* **1964**, *86*, 3759-3767.
17. Parker, D. *J. Chem. Soc., Perkin Trans 2*, **1983**, 83-88.

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